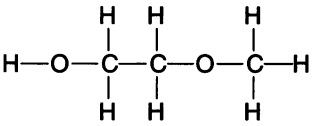
Comparison of Reproductive Responses of Different Strains (3 Studies)–III

Ethylene Glycol Monomethyl Ether



CAS #109-86-4
C3H mice, at 0.0, 0.03, 0.1, 0.3%, drinking water
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Ethylene glycol monomethyl ether (EGME), a common chemical and solvent used in industry and in consumer goods, was used to test the hypothesis that mouse strains of differing basal fertility would respond differently to a reproductive toxicant (Chapin et al., Fundam Appl Toxicol 21:8–14 [1993]). This study used C57Bl/6 mice in a modified RACB protocol. The design was modified to use 30 pairs of mice per group instead of the usual 40 per control and 20 per treated group. Neither Task 3, the crossover mating test, nor Task 1, normally used to set doses for the continuous cohabitation phase, was conducted, because sufficient data were already available on affected sex and the optimal doses to use. In all three studies, dose levels of EGME in drinking water for Task 2 were set at 0.03, 0.1, and 0.3% EGME, weight per volume. These concentrations produced estimated consumption values of approximately 60, 220, and 630 mg/kg/day. Water consumption was not reduced by EGME addition. Twelve mice died on study: one control male, one male and one female at 0.03%, three males and two females at 0.1%, and three females at 0.3%. These deaths were not judged to be treatment related.

No high dose pairs in Task 2 (the continuous cohabitation phase of the study) delivered any pups, live or dead. In the middle dose group, the fertility index (the proportion of cohabiting pairs delivering at least one litter) was not different from controls. For control pairs, the mean number of litters per fertile pair was 3.3, with a mean of 5.3 pups per litter. While EGME at 0.1 or 0.03% did not change the mean litters per pair, it reduced the number of live pups per litter at 0.1% to 2.97, and reduced the proportion of pups born alive from 81 (control) to 52% (at 0.1% EGME).

The number of pairs delivering a fourth litter was 15, 14, and 6 for control, low, and middle dose EGME, respectively; the numbers delivering a fifth litter were 3, 3, and 2, respectively. The proportion of stillbirths rose in the middle dose group, from a control value of 29% to 63%. This was aggravated by an increase in the proportion of stillbirths, which rose in the middle dose group from a control value of 29% to 63%. Thus, only 8, 6, and 2 pairs had litters of live pups for evaluating the second generation in the control, low, and middle dose groups, respectively. While postnatal mortality was not increased in this strain by EGME, male pup weight gain was significantly reduced, and pairwise comparisons with the controls showed reduced male pup weight at all times after postnatal day 1. At weaning, this weight was 35% less than controls.

After the F_1s were weaned, all remaining F_0 mice were killed and necropsied. Female body weight was reduced at the top dose by approximately 9%. Relative female liver weight was increased by 6, 6, and 2% in the low to high dose groups, respectively. Relative kidney weight was increased in the high dose females by 8%. In high dose males, body weight was reduced by 7%, while absolute testis weight was reduced by 51% and relative epididymis weight was reduced by 25%. The percentage of motile epididymal sperm was reduced by 8 and 72% at the middle and high dose levels, respectively. In the high dose group, epididymal sperm density was reduced by 60%, and the percentage of abnormal forms increased from a control value of 5 to 50% abnormals.

At 74 ± 10 days of age, F_1 mice were cohabited for a week within treatment groups. Due to poor fertility, there were 11, 15, and 5 pairs for the control, low dose, and middle dose groups, respectively. At the middle dose level, no pairs mated or delivered any young. These mating and fertility indices were not affected at the low dose. The low dose also did not differ from controls in the number of live pups per litter, the proportion born alive, their sex ratio, or the absolute or adjusted pup weights.

After the F_2 pups were born and assessed, all the mice were killed, and the F_1 mice necropsied. While the low dose females were not different from controls, the middle dose females weighed 23% less than controls. While male mice body weights were not affected by EGME consumption, relative liver weight was increased by 10% in the middle dose group, and kidney weights were increased by 5 and 17% in the low and middle dose groups, respectively. Absolute testis weight was reduced by 33% at the middle dose level, and relative epididymis weight reduced by 23%. Also at the middle dose level, epididymal sperm density was reduced by 50% and the percentage of abnormal forms increased from a control level of 4% to 25%.

This strain had the lowest fertility of the three strains tested: an average of 3.3 litters per pair, and approximately five pups per litter (vs 3.5 and 8 for the C57s, and 4.7 and 12 for the Swiss CD-1s, respectively). EGME at 0.3% had the greatest adverse effect on the C3H, with no litters of any pups, live or dead, delivered at that dose. While the C57 mice showed greater changes in the second generation and in some necropsy end points (prostate and seminal vesicle weights, and epididymal sperm count) compared to the C3H, both these strains were more affected by EGME than were the Swiss mice.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB88192240**
Chemical: **Ethylene Glycol Monomethyl Ether**
CAS#: **109-86-4**
Mode of exposure: **Drinking water**
Species/strain: **C3H mice**

F_0 generation — Dose concentration →	0.03%	0.1%	0.3%
General toxicity	Male, female	Male, female	Male, female
Body weight	—, —	—, —	↓, ↓
Kidney weight[a]	—, —	—, —	—, ↑
Liver weight[a]	—, ↑	—, ↑	—, —
Mortality	—, —	—, —	—, ↑
Feed consumption	•, •	•, •	•, •
Water consumption	—, —	—, —	—, —
Clinical signs	—, —	—, —	—, —
Reproductive toxicity			
x̄ litters/pair	—	—	•
# live pups/litter; pup wt./litter	—, —	↓, —	•, •
Cumulative days to litter	—	•	•
Absolute testis, epididymis weight[a]	—, —	—, —	↓, ↓
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, —	—, —	—, —
Epidid. sperm parameters (#, motility, morphology)	—, —, —	—, ↓, —	↓, ↓, ↑
Estrous cycle length	•	•	•

Determination of affected sex (crossover)	Male	Female	Both
Dose level	•	•	•

F_1 generation — Dose concentration →	0.03%	0.1%	•
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	—, —	—, —	•
Mortality	—, —	—, —	•
Adult body weight	—, —	—, ↓	•
Kidney weight[a]	↑, —	↑, —	•
Liver weight[a]	—, —	↑, —	•
Feed consumption	•	•	•
Water consumption	—, —	↓, ↓	•
Clinical signs	—, —	—, —	•
Reproductive toxicity			
Fertility index	—	↓	•
# live pups/litter; pup wt./litter	—, —	—, —	•, •
Absolute testis, epididymis weight[a]	—, —	↓, ↓	•, •
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, —	—, —	•, •
Epidid. sperm parameters (#, motility, morphology)	—, —, —	↓, —, ↑	•, •, •
Estrous cycle length	•	•	•

Summary information	
Affected sex?	Both
Study confounders:	None
F_1 more sensitive than F_0?	Unclear
Postnatal toxicity:	Yes

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); —, —, no change in males or females. [a]Adjusted for body weight.